CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074839

Trade Name : ETODOLAC TABLETS

Generic Name: Etodolac Tablets 400mg

Sponsor : Geneva Pharmaceuticals, Inc.

Approval Date: July 11, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074839

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074839

APPROVAL LETTER

ANDA 74-839

JUL 11 1997

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

Dear Madam:

This is in reference to your abbreviated new drug application dated January 31, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Etodolac Tablets, 400 mg.

Reference is also made to your amendments dated July 11 and October 11, 1996; and February 13, April 4, May 5, June 3 and 19, and July 8, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Etodolac Tablets, 400 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Lodine® Tablets, 400 mg of Wyeth-Ayerst Laboratories, Inc. Your dissolution testing should be incorporated into the stability and quality control programs using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

7-11-97

Mar 30

Etodolac Tablets

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

90 TABLETS

Geneva pharmaceuticals, inc.

N 3 0781-1234-31 1

Each tablet contains: Etodolac 400 mg

Usual Dosage: See package insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

ISS 95-12M N96/7

Manufactured By
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

LOT:

EXP.:

JUL 1 1 1997

Etodolac Tablets

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

Geneva pharmaceuticals, inc.

N 3 0781-1234-01 4

Each tablet contains: Etodolac 400 mg

Usual Dosage: See package insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container. **KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.**

ISS 95-12M N96/7

Manufactured By
Geneva Pharmaceuticals, Inc
Broomfield, CO 80020

LOT:

EXP.

JUL 1 1 1997

Etodolac Tablets

400 mg

CAUTION: Federal law prohibits dispensing without prescription.

500 TABLETS

Geneva pharmaceuticals, inc.

N 3 0781-1234-05 2

Each tablet contains:
Etodolac 400 mg

Usual Dosage: See package insert.

Store at controlled room temperature 15°-30°C (59°-86°F).

Dispense in a tight, light-resistant container.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

ISS 95-12M N96/7

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

LOT:

EXP.:

JUL 1 1 1997

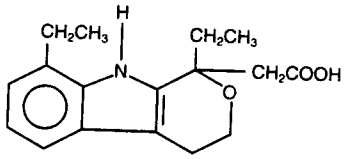
133b

7186

ETODOLAC TABLETS

7186-3

DESCRIPTION: Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. The structural formula for etodolac is:



$C_{17}H_{21}NO_3$ M.W. 287.37

It has a pKa of 4.65 and an n-octanol:water partition coefficient of 11.4 at pH 7.4. Etodolac is a white crystalline compound, insoluble in water but soluble in alcohols, chloroform, dimethyl sulfoxide, and aqueous polyethylene glycol.

Each tablet, for oral administration, contains 400 mg of etodolac. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, polysorbate 80, titanium dioxide, and triacetin.

CLINICAL PHARMACOLOGY:

Pharmacology: Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of etodolac, like that of other NSAIDs, is not known but is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac is a racemic mixture of [-] R- and [+] S-etodolac. As with other NSAIDs, it has been demonstrated in animals that the [+] S-form is biologically active. Both enantiomers are stable and there is no [-] R to [+] S conversion *in vivo*.

Pharmacodynamics: Analgesia was demonstrable 1/2 hour following single doses of 200 to 400 mg etodolac, with the peak effect occurring in 1 to 2 hours. The analgesic effect generally lasted for 4 to 6 hours (see Clinical Trials).

Pharmacokinetics: The pharmacokinetics of etodolac have been evaluated in 267 normal subjects, 44 elderly patients (>65 years old), 19 patients with renal failure (creatinine clearance 37 to 88 mL/min), 9 patients on hemodialysis, and 10 patients with compensated hepatic cirrhosis.

Etodolac, when administered orally, exhibits kinetics that are well described by a two-compartment model with first-order absorption.

Etodolac has no apparent pharmacokinetic interaction when administered with phenytoin, glyburide, furosemide or hydrochlorothiazide.

Absorption: Etodolac is well absorbed and had a relative bioavailability of 100% when 200 mg capsules were compared with a solution of etodolac. Based on mass balance studies, the systemic availability of etodolac from either the tablet or capsule formulation, is at least 80%. Etodolac does not undergo significant first-pass metabolism following oral administration. Mean (± 1 SD) peak plasma concentrations range from approximately 14 ± 4 to 37 ± 9 µg/mL after 200 to 600 mg single doses and are reached in 80 ± 30 minutes (see Table 1 for summary of pharmacokinetic parameters). The dose-proportionality based on AUC (the area under the plasma concentration-time curve) is linear following doses up to 600 mg every 12 hours. Peak concentrations are dose-proportional for both total and free etodolac following doses up to 400 mg every 12 hours, but following a 600 mg dose, the peak is about 20% higher than predicted on the basis of lower doses.

Table 1
Etodolac Steady-State Pharmacokinetic Parameters (N=267)

Kinetic Parameters	Mean ± SD
Extent of oral absorption (bioavailability)[F]	≥ 80%
Oral-dose clearance [CL/F]	47 ± 16 mL/h/kg
Steady-state volume [V_{ss}/F]	362 ± 129 mL/kg
Distribution half-life [$t_{1/2}$, α]	0.71 ± 0.50 h
Terminal half-life [$t_{1/2}$, β]	7.3 ± 4.0 h

Antacid Effects: The extent of absorption of etodolac is not affected when etodolac is administered with an antacid. Coadministration with an antacid decreases the peak concentration reached by about 15 to 20%, with no measurable effect on time-to-peak.

Food Effects: The extent of absorption of etodolac is not affected when etodolac is administered after a meal. Food intake, however, reduces the peak concentration reached by approximately one half and increases the time-to-peak concentration by 1.4 to 3.8 hours.

Distribution: Etodolac has an apparent steady-state volume of distribution about 0.362 L/kg. Within the therapeutic dose range, etodolac is more than 99% bound to plasma proteins. The free fraction is less than 1% and is independent of etodolac total concentration over the dose range studied.

Metabolism: Etodolac is extensively metabolized in the liver, with renal elimination of etodolac and its metabolites being the primary route of excretion. The inter-subject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

Protein Binding: Data from *in vitro* studies, using peak serum concentrations at reported therapeutic doses in humans, show that the etodolac free fraction is not significantly altered by acetaminophen, ibuprofen, indomethacin, naproxen, piroxicam, chlorpropamide, glipizide, glyburide, phenytoin, and probenecid.

Elimination: The mean plasma clearance of etodolac, following oral dosing is 47 (± 16) mL/h/kg, and terminal disposition half-life is 7.3 (± 4.0) hours. Approximately 72% of the administered dose is recovered in the urine as

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–etodolac, unchanged	1%
–etodolac glucuronide	13%
–hydroxylated metabolites (6-, 7-, and 8-OH)	5%
–hydroxylated metabolite glucuronides	20%
–unidentified metabolites	33%

Fecal excretion accounted for 16% of the dose.

Special Populations:

Elderly Patients: In clinical studies, etodolac clearance was reduced by about 15% in older patients (> 65 years of age). In these studies, age was shown not to have any effect on etodolac half-life or protein binding, and there was no change in expected drug accumulation. No dosage adjustment is generally necessary in the elderly on the basis of pharmacokinetics. The elderly may need dosage adjustment, however, on the basis of body size (see PRECAUTIONS: Geriatric Population), as they may be more sensitive to antiprostaglandin effects than younger patients (see PRECAUTIONS: Geriatric Population).

Renal Impairment: Studies in patients with mild-to-moderate renal impairment (creatinine clearance 37 to 88 mL/min) showed no significant differences in the disposition of total and free etodolac. In patients undergoing hemodialysis, there was a 50% greater apparent clearance of total etodolac, due to a 50% greater unbound fraction. Free etodolac clearance was not altered, indicating the importance of protein binding in etodolac's disposition. Nevertheless, etodolac is not dialyzable.

Hepatic Impairment: In patients with compensated hepatic cirrhosis, the disposition of total and free etodolac is not altered. Although no dosage adjustment is generally required in this patient population, etodolac clearance is dependent on hepatic function and could be reduced in patients with severe hepatic failure.

Clinical Trials:

Analgesia: Controlled clinical trials in analgesia were single-dose, randomized, double-blind, parallel studies in three pain models, including dental extractions. The analgesic effective dose for etodolac established in these acute pain models was 200 to 400 mg. The onset of analgesia occurred approximately 30 minutes after oral administration. Etodolac 200 mg provided efficacy comparable to that obtained with aspirin (650 mg). Etodolac 400 mg provided efficacy comparable to that obtained with acetaminophen with codeine (600 mg + 60 mg). The peak analgesic effect was between 1 to 2 hours. Duration of relief averaged 4 to 5 hours for 200 mg of etodolac and 5 to 6 hours for 400 mg of etodolac as measured by when approximately half of the patients required remedication.

Osteoarthritis: The use of etodolac in managing the signs and symptoms of osteoarthritis of the hip or knee was assessed in double-blind, randomized, controlled clinical trials in 341 patients. In patients with osteoarthritis of the knee, etodolac, in doses of 600 to 1000 mg/day, was better than placebo in two studies. The clinical trials in osteoarthritis used b.i.d. dosage regimens.

INDICATIONS AND USAGE: Etodolac is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis. Etodolac is also indicated for the management of pain.

CONTRAINDICATIONS: Etodolac is contraindicated in patients with known hypersensitivity to etodolac. Etodolac should not be given to patients who have experienced asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to etodolac have been reported in such patients (see WARNINGS: Anaphylactoid Reactions).

WARNINGS: Risk of Gastrointestinal (GI) Ulceration, Bleeding, and Perforation with Nonsteroidal, Anti-Inflammatory Drug (NSAID) Therapy: Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur at any time, with or without warning symptoms, in patients treated chronically with NSAIDs. Although minor upper GI problems, such as dyspepsia, are common, usually developing early in therapy, physicians should remain alert for ulceration and bleeding in patients treated chronically with NSAIDs, even in the absence of previous GI-tract symptoms. In patients observed in clinical trials of such agents for several months' to 2 years' duration, symptomatic upper GI ulcers, gross bleeding, or perforation appears to occur in approximately 1% of patients treated for 3 to 6 months and in about 2% to 4% of patients treated for 1 year. Physicians should inform patients about the signs and/or symptoms of serious GI toxicity and what steps to take if they occur.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Except for a prior history of serious GI events and other risk factors known to be associated with peptic ulcer disease, such as alcoholism, smoking, etc., no risk factors (e.g., age, sex) have been associated with increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less well than other individuals, and most spontaneous reports of fatal GI events are in this population. Studies to date are inconclusive concerning the relative risk of various NSAIDs in causing such reactions. High doses of any NSAID probably carry a greater risk of these reactions, although controlled clinical trials showing this do not exist in most cases. In considering the use of relatively large doses (within the recommended dosage range), sufficient benefit should be anticipated to offset the potential increased risk of GI toxicity.

Anaphylactoid Reactions: Anaphylactoid reactions may occur in patients without prior exposure to etodolac. Etodolac should not be given to patients with the aspirin triad. The triad typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking aspirin or other nonsteroidal anti-inflammatory drugs. Fatal reactions have been reported in such patients (see CONTRAINDICATIONS and PRECAUTIONS: Pre-existing Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease: In cases with advanced kidney disease, as with other NSAIDs, treatment with etodolac should only be initiated with close monitoring of the patient's kidney function (see PRECAUTIONS: Renal Effects).

Pregnancy: In late pregnancy, as with other NSAIDs, etodolac should be avoided because it may cause premature closure of the ductus arteriosus (see PRECAUTIONS: Teratogenic Effects: Pregnancy Category C).

PRECAUTIONS:

General Precautions:

Renal Effects: As with other NSAIDs, long-term administration of etodolac to rats has resulted in renal papillary necrosis and other renal medullary changes. Renal pelvic transitional epithelial hyperplasia, a spontaneous change occurring with variable frequency, was observed with increased frequency in treated male rats in a 2-year chronic study.

A second form of renal toxicity encountered with etodolac, as with other NSAIDs, is seen in patients with conditions in which renal prostaglandins have a supportive role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, or liver dysfunction; those taking diuretics; and the elderly. Discontinuation of nonsteroidal anti-inflammatory drug therapy is usually followed by recovery to the pretreatment state.

Etodolac metabolites are eliminated primarily by the kidneys. The extent to which the inactive glucuronide metabolites may accumulate in patients with renal failure has not been studied. As with other drugs whose metabolites are excreted by the kidney, the possibility that adverse reactions (not listed in ADVERSE REACTIONS) may be attributable to these metabolites should be considered.

Hepatic Effects: Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs including etodolac. These abnormalities may disappear, remain essentially unchanged, or progress with continued therapy. Meaningful elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with etodolac. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with etodolac. Rare cases of liver necrosis and hepatic failure, some of them with fatal outcomes have been reported. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), etodolac should be discontinued.

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Hematological Effects: Anemia is sometimes seen in patients receiving NSAIDs including etodolac. This may be due to fluid retention, GI blood loss, or an incompletely described effect upon erythropoiesis. Patients on long-term treatment with NSAIDs, including etodolac, should have their hemoglobin or hematocrit checked if they exhibit signs or symptoms of anemia.

All drugs which inhibit the biosynthesis of prostaglandins may interfere to some extent with platelet function and vascular responses to bleeding.

Fluid Retention and Edema: Fluid retention and edema have been observed in some patients taking NSAIDs, including etodolac. Therefore, etodolac should be used with caution in patients with fluid retention, hypertension, or heart failure.

Pre-existing Asthma: About 10% of patients with asthma may have aspirin-sensitive asthma. The use of aspirin in patients with aspirin-sensitive asthmas has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between aspirin and other nonsteroidal anti-inflammatory drugs has been reported in such aspirin-sensitive patients, etodolac should not be administered to patients with this form of aspirin sensitivity and should be used with caution in all patients with pre-existing asthma.

Information for Patients: Etodolac, like other drugs of its class, can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. Physicians may wish to discuss with their patients the potential risks (see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS) and likely benefits of nonsteroidal anti-inflammatory drug treatment.

Patients on etodolac should report to their physicians signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

Because serious gastrointestinal tract ulcerations and bleeding can occur without warning symptoms, physicians should follow chronically treated patients for the signs and symptoms of ulcerations and bleeding and should inform them of the importance of this follow-up (see WARNINGS: Risk of GI Ulceration, Bleeding and Perforation with Nonsteroidal, Anti-Inflammatory (NSAID) Therapy).

Patients should also be instructed to seek medical emergency help in case of an occurrence of anaphylactoid reactions (see WARNINGS).

Laboratory Tests: Patients on long-term treatment with etodolac, as with other NSAIDs, should have their hemoglobin or hematocrit checked periodically for signs or symptoms of anemia. Appropriate measures should be taken in case such signs of anemia occur.

If clinical signs and symptoms consistent with liver disease develop or if systemic manifestations occur (e.g., eosinophilia, rash, etc.) and if abnormal liver tests are detected, persist or worsen, etodolac should be discontinued.

(See Reverse)

Drug Interactions:
Antacids: The concomitant administration of antacids has no apparent effect on the extent of absorption of etodolac. However, antacids can decrease the peak concentration reached by 15% to 20% but have no detectable effect on the time-to-peak.
Aspirin: When etodolac is administered with aspirin, its protein binding is reduced, although the clearance of free etodolac is not altered. The clinical significance of this interaction is not known; however, as with other NSAIDs, concomitant administration of etodolac and aspirin is not generally recommended because of the potential of increased adverse effects.
Warfarin: Short-term pharmacokinetic studies have demonstrated that concomitant administration of warfarin and etodolac results in reduced protein binding of warfarin, but there was no change in the clearance of free warfarin. There was no significant difference in the pharmacodynamic effect of warfarin administered alone and warfarin administered with etodolac as measured by prothrombin time. Thus, concomitant therapy with warfarin and etodolac should not require dosage adjustment of either drug. However, there have been a few spontaneous reports of prolonged prothrombin times in etodolac-treated patients receiving concomitant warfarin therapy. Caution should be exercised because interactions have been seen with other NSAIDs.
Cyclosporine, Digoxin, Lithium, Methotrexate: Etodolac, like other NSAIDs, through effects on renal prostaglandins, may cause changes in the elimination of these drugs leading to elevated serum levels of digoxin, lithium, and methotrexate and increased toxicity. Nephrotoxicity associated with cyclosporine may also be enhanced. Patients receiving these drugs who are given etodolac, or any other NSAID, and particularly those patients with altered renal function, should be observed for the development of the specific toxicities of these drugs.
Phenylbutazone: Phenylbutazone causes increase (by about 80%) in the free fraction of etodolac. Although *in vivo* studies have not been done to see if etodolac clearance is changed by coadministration of phenylbutazone, it is not recommended that they be coadministered.
Drug/Laboratory Test Interactions: The urine of patients who take etodolac can give a false-positive reaction for urinary bilirubin (urobilin) due to the presence of phenolic metabolites of etodolac. Diagnostic dip-stick methodology, used to detect ketone bodies in urine, has resulted in false-positive findings in some patients treated with etodolac. Generally, this phenomenon has not been associated with other clinically significant events. No dose relationship has been observed.

Etodolac treatment is associated with a small decrease in serum uric acid levels. In clinical trials, mean decreases of 1 to 2 mg/dL were observed in arthritic patients receiving etodolac (600 mg to 1000 mg/day) after 4 weeks of therapy. These levels then remained stable for up to 1 year of therapy.
Carcinogenesis, Mutagenesis, and Impairment of Fertility: No carcinogenic effect of etodolac was observed in mice or rats receiving oral doses of 15 mg/kg/day (45 to 89 mg/m^2, respectively) or less for periods of 2 years or 18 months, respectively. Etodolac was not mutagenic in *in vitro* tests performed with *S. typhimurium* and mouse lymphoma cells as well as in an *in vivo* mouse micronucleus test. However, data from the *in vitro* human peripheral lymphocyte test showed an increase in the number of gaps (3.0 to 5.3% unstained regions in the chromatid without dislocation) among the etodolac-treated cultures (50 to 200 µg/mL) compared to negative controls (2.0%); no other difference was noted between the controls and drug-treated groups. Etodolac showed no impairment of fertility in male and female rats up to oral doses of 16 mg/kg (94 mg/m^2). However, reduced implantation of fertilized eggs occurred in the 8 mg/kg group.
Pregnancy: *Teratogenic Effects:* Pregnancy Category C: In teratology studies, isolated occurrences of alterations in limb development were found and included polydactyly, oligodactyly, syndactyly, and unossified phalanges in rats and oligodactyly and synostosis of metatarsals in rabbits. These were observed at dose levels (2 to 14 mg/kg/day) close to human clinical doses. However, the frequency and the dosage group distribution of these findings in initial or repeated studies did not establish a clear drug or dose-response relationship.

There are no adequate or well-controlled studies in pregnant women. Etodolac should be used during pregnancy only if the potential benefits justify the potential risk to the fetus. Because of the known effects of NSAIDs on parturition and on the human fetal cardiovascular system with respect to closure of the ductus arteriosus, use during late pregnancy should be avoided.
Labor and Delivery: In rat studies with etodolac, as with other drugs known to inhibit prostaglandin synthesis, an increased incidence of dystocia, delayed parturition, and decreased pup survival occurred. The effects of etodolac on labor and delivery in pregnant women are unknown.
Nursing Mothers: It is not known whether etodolac is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from etodolac, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.
Pediatric Use: Safety and effectiveness in pediatric patients have not been established.
Geriatric Population: As with any NSAID, however, caution should be exercised in treating the elderly, and when individualizing their dosage, extra care should be taken when increasing the dose because the elderly seem to tolerate NSAID side effects less well than younger patients. In patients 65 years and older, no substantial differences in the side effect profile of etodolac were seen compared with the general population (see CLINICAL PHARMACOLOGY: Pharmacokinetics).
ADVERSE REACTIONS: Adverse-reaction information for etodolac was derived from 2,629 arthritic patients treated with etodolac in double-blind and open-label clinical trials of 4 to 320 weeks in duration and worldwide postmarketing surveillance studies. In clinical trials, most adverse reactions were mild and transient. The discontinuation rate in controlled clinical trials, because of adverse events, was up to 10% for patients treated with etodolac.

New patient complaints (with an incidence greater than or equal to 1%) are listed below by body system. The incidences were determined from clinical trials involving 465 patients with osteoarthritis treated with 300 to 500 mg of etodolac b.i.d. (i.e., 600 to 1000 mg/day).
Incidence Greater Than or Equal to 1%: Probably Causally Related:
Body as a whole: Chills and fever.
Digestive system: Dyspepsia (10%), abdominal pain*, diarrhea*, flatulence*, nausea*, constipation, gastritis, melena, vomiting.
Nervous system: Asthenia/malaise*, dizziness*, depression, nervousness.
Skin and appendages: Pruritus, rash.
Special senses: Blurred vision, tinnitus.
Urogenital system: Dysuria, urinary frequency.
*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked.
Incidence Less Than 1%: Probably Causally Related (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized):
Body as a whole: Allergic reaction, anaphylactoid reaction.
Cardiovascular system: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*
Digestive system: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*
Hemic and lymphatic system: Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*
Metabolic and nutritional: Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*
Nervous system: Insomnia, somnolence.
Respiratory system: Asthma.
Skin and appendages: Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome,* hyperpigmentation, *erythema multiforme.*
Special senses: Photophobia, transient visual disturbances.
Urogenital system: Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.
Incidence Less Than 1%: Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians):
Body as a whole: Infection, headache.
Cardiovascular system: Arrhythmias, myocardial infarction, cerebrovascular accident.
Digestive system: Esophagitis with or without stricture or cardiospasm, colitis.

Nervous System: Asthenia, malaise, dizziness, depression, nervousness.
Skin and appendages: Pruritus, rash.
Special senses: Blurred vision, tinnitus.
Urogenital system: Dysuria, urinary frequency.
*Drug-related patient complaints occurring in 3 to 9% of patients treated with etodolac.

Drug-related patient-complaints occurring in fewer than 3%, but more than 1%, are unmarked.

Incidence Less Than 1%: Probably Causally Related (Adverse reactions reported only in worldwide postmarketing experience, not seen in clinical trials, are considered rarer and are italicized):

Body as a whole: Allergic reaction, anaphylactoid reaction.
Cardiovascular system: Hypertension, congestive heart failure, flushing, palpitations, syncope, *vasculitis (including necrotizing and allergic).*
Digestive system: Thirst, dry mouth, ulcerative stomatitis, anorexia, eructation, elevated liver enzymes, *cholestatic hepatitis,* hepatitis, *cholestatic jaundice, duodenitis, jaundice, hepatic failure, liver necrosis,* peptic ulcer with or without bleeding and/or perforation, *intestinal ulceration, pancreatitis.*
Hemic and lymphatic system: Ecchymosis, anemia, thrombocytopenia, bleeding time increased, *agranulocytosis, hemolytic anemia, leukopenia, neutropenia, pancytopenia.*
Metabolic and nutritional: Edema, serum creatinine increase, *hyperglycemia in previously controlled diabetic patients.*
Nervous system: Insomnia, somnolence.
Respiratory system: Asthma.
Skin and appendages: Angioedema, sweating, urticaria, vesiculobullous rash, *cutaneous vasculitis with purpura, Stevens-Johnson Syndrome,* hyperpigmentation, *erythema multiforme.*
Special senses: Photophobia, transient visual disturbances.
Urogenital system: Elevated BUN, renal failure, renal insufficiency, renal papillary necrosis.

Incidence Less Than 1%: Causal Relationship Unknown (Medical events occurring under circumstances where causal relationship to etodolac is uncertain. These reactions are listed as alerting information for physicians):

Body as a whole: Infection, headache.
Cardiovascular system: Arrhythmias, myocardial infarction, cerebrovascular accident.
Digestive system: Esophagitis with or without stricture or cardiospasm, colitis.
Metabolic and nutritional: Change in weight.
Nervous system: Paresthesia, confusion.
Respiratory system: Bronchitis, dyspnea, pharyngitis, rhinitis, sinusitis.
Skin and appendages: Alopecia, maculopapular rash, photosensitivity, skin peeling.
Special senses: Conjunctivitis, deafness, taste perversion.
Urogenital system: Cystitis, hematuria, leukorrhea, renal calculus, interstitial nephritis, uterine bleeding irregularities.

OVERDOSAGE: Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur and coma has occurred following massive ibuprofen or mefenamic-acid overdose. Hypertension, acute renal failure, and respiratory depression may occur but are rare. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following overdose.

Patients should be managed by symptomatic and supportive care following an NSAID overdose. There are no specific antidotes. Gut decontamination may be indicated in patients seen within 4 hours of ingestion with symptoms or followng a large overdose (5 to 10 times the usual dose). This should be accomplished via emesis and/or activated charcoal (60 to 100 g in adults, 1 to 2 g/kg in children) with an osmotic cathartic. Forced diuresis, alkalinization of the urine, hemodialysis, or hemoperfusion would probably not be useful due to etodolac's high protein binding.

DOSAGE AND ADMINISTRATION: As with other NSAIDs, the lowest dose and longest dosing interval should be sought for each patient. Therefore, after observing the response to initial therapy with etodolac, the dose and frequency should be adjusted to suit an individual patient's needs.

Dosage adjustment of etodolac is generally not required in patients with mild to moderate renal impairment. Etodolac should be used with caution in such patients, because, as with other NSAIDs, it may further decrease renal function in some patients with impaired renal function (see PRECAUTIONS: General Precautions: Renal Effects).

Analgesia: The recommended total daily dose of etodolac for acute pain is up to 1000 mg, given as 200-400 mg every 6 to 8 hours. In some patients, if the potential benefits outweigh the risks; the dose may be increased to 1200 mg/day in order to achieve a therapeutic benefit that might not have been achieved with 1000 mg/day. Doses of etodolac greater than 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

Osteoarthritis: The recommended starting dose of etodolac for the management of the signs and symptoms of osteoarthritis is: 300 mg b.i.d., t.i.d., or 400 mg b.i.d., or 500 mg b.i.d. During long-term administration, the dose of etodolac may be adjusted up or down depending on the clinical response of the patient. A lower dose of 600 mg/day may suffice for long-term administration. In patients who tolerate 1000 mg/day, the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required. When treating patients with higher doses, the physician should observe sufficient increased clinical benefit to justify the higher dose. Physicians should be aware that doses above 1000 mg/day have not been adequately evaluated in well-controlled clinical trials.

In chronic conditions, a therapeutic response to therapy with etodolac is sometimes seen within one week of therapy, but most often is observed by two weeks. After a satisfactory response has been achieved, the patient's dose should be reviewed and adjusted as required.

HOW SUPPLIED: Etodolac tablets, for oral administration, are provided in bottles of 30, 100, and 500 as:

400 mg: white, round, unscored tablets debosssed GG 774 on one side and plain on the reverse side, film-coated white.

Store at controlled room temperature 15º-30ºC (59º-86ºF).

Dispense in a tight, light-resistant container.

Caution: Federal law prohibits dispensing without prescription.

Rev. 97-3M C97/4
7186-3

Manufactured By
Geneva Pharmaceuticals, Inc.
Broomfield, CO 80020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074839

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO 3 (revision 2)

2. ANDA 74-839

3. NAME AND ADDRESS OF APPLICANT
Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. Box 446
Broomfield, CO 80038-0446

4. LEGAL BASIS FOR SUBMISSION
Lodine® (Wyeth-Ayerst). Patent expired 02/28/97.
Exclusivity for new indication (rheumatoid arthritis) expires 06/28/1999.

5. SUPPLEMENT(s) N/A 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME Etodolac Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

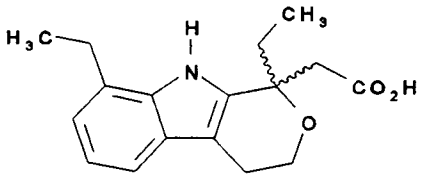
9. AMENDMENTS AND OTHER DATES: See next page

10. PHARMACOLOGICAL CATEGORY NSAID 11. Rx or OTC Rx

12. RELATED IND/NDA/DMF(s) [redacted](b)4 -[redacted]

13. DOSAGE FORM Tablets 14. POTENCY 400 mg

15. CHEMICAL NAME AND STRUCTURE



(±)-1,8-Diethyl-1,3,4,9-tetrahydropyrano[3,4-b]indole-1-acetic acid

$C_{17}H_{21}NO_3$ [*41340-25-4*]
M.W. = 287.36

16. RECORDS AND REPORTS N/A

17. COMMENTS No remaining chemistry deficiencies.

18. CONCLUSIONS AND RECOMMENDATIONS
Recommend: APPROVAL.

19. REVIEWER: J.L. Smith DATE COMPLETED: April 10 & May 19 & June 24, 1997

cc: ANDA 74-839
DIV FILE

Endorsements:
HFD-623/J.Smith/[redacted]/S/
HFD-623/V.Sayeed
Y:\NEW\FIRMSAM\GENEVA\LTRS&REV\74839AP3.CD2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074839

BIOEQUIVALENCE REVIEW(S)

02

ANDA 74-839

SEP 30 1996

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2655 W. Midway Blvd.
P.O. BOX 446
Broomfield CO 80038-0446

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Etodolac Tablets 400 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

   The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

   Not less than h\z of the labeled amount of etodolac in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 27 1996

Etodolac
400 mg Tablets
ANDA #74-839
Reviewer: Kuldeep R. Dhariwal
Filename: 74839SD.796

Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446
Submission Date:
July 11, 1996

Response to Review of Bioequivalence Studies and Dissolution Data

Background:

Geneva Pharmaceuticals, Inc. Previously submitted a single-dose *in vivo* bioequivalence study under fasting and fed conditions and dissolution data comparing its etodolac tablets, 400 mg with Wyeth-Ayerst's Lodine® tablets, 400 mg (Filename: 74839SD.196; submission date: January 31, 1996). The bioequivalence studies conducted by the firm were found acceptable to the Division of Bioequivalence. The dissolution testing was, however, not acceptable. The dissolution testing was done using apparatus 2 (paddles) at 50 rpm and 1000 mL of 0.05 M pH 7.5 phosphate buffer as medium. There is no USP method available for dissolution testing of etodolac tablets. The agency recommends the use of basket and a speed of 100 rpm. Following comment was sent to the firm on May 21, 1996:

Dissolution should be repeated on 12 individual dosage units of the test and reference products using apparatus I (basket) at 100 rpm and all other conditions the same.

The firm submitted the response as amendment on July 11, 1996 which was received by the Office of Generic Drugs on July 12, 1996. The amendment was given to this reviewer on July 22, 1996.

Response:

The dissolution testing was done using non-USP, FDA method: apparatus 1 (basket) at 100 rpm and 1000 mL of 0.05 M pH 7.5 phosphate buffer. The firm has provided the comparative 12 unit dissolution data on both the test and reference products.

Comments:

1. The dissolution testing on test and reference products was done using the method recommended by the agency. Lot numbers of both test and reference drug products are the same as used for bioequivalence study.

2. The dissolution of both products is better than the previously submitted data. This is probably due to the use of basket at 100 rpm over paddles at 50 rpm. The test product dissolves much faster than the reference product. Both products meet the specification of not less than [illegible] in 30 minutes.

3. The dissolution data are acceptable.

Recommendation:

1. The dissolution testing data conducted by Geneva Pharmaceuticals, Inc., on its etodolac tablets, 400 mg, lot #6495044 is acceptable. The firm has previously conducted an acceptable *in vivo* Bioequivalence study (submission dated January 31, 1996), comparing the test product with Wyeth-Ayerst's Lodine® tablets, 400 mg, lot #9941383. The firm's etodolac tablet, 400 mg is deemed bioequivalent to Lodine®, 400 mg tablet manufactured by Wyeth-Ayerst.

2. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 1000 mL of 0.05 M phosphate buffer, pH 7.5 at 37°C using apparatus 1 (basket) at 100 rpm. The test product should meet the following specifications:

> Not less than [illegible] of the labeled amount of etodolac in the dosage form is dissolved in 30 minutes.

3. From the Bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing, and the application is acceptable.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR

/S/

Date 9/5/1996

/S/

Concur: _____ Date 9/27/96

Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74839 (original, duplicate), Dhariwal, HFD-655 (Nerurkar), Drug File, Division File

Draft: 072396; Final: 090496

Table 1. *In Vitro* Dissolution Testing

Drug (Generic Name): Etodolac Tablets
Dose Strength: 400 mg
ANDA No.: 74-839
Firm: Geneva Pharmaceuticals, Inc.
Submission Date: July 11, 1996
File Name: 74839SD.796

I. Conditions for Dissolution Testing:

USP XXIII Basket: X Paddle: RPM: 100
No. Units Tested: 12
Medium: 0.05 M phosphate buffer, pH 7.5 Volume: 1000 mL
Specifications: NLT (b)4 (Q) in 20 minutes
Reference Drug: Lodine® Tablets (Wyeth Ayerst)
Assay Methodology: (b)4 -

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6495044 Strength(mg) 400			Reference Product Lot # 9941383 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
5	104		1.0	37		20.5
10	104	(b)4 -	1.1	75	(b)4 -	14.3
15	104	nfiden	1.3	92	nfident	12.7
20	105	usines	1.0	100	Busines	4.7
30	104		0.8	105		0.9

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

ANDA 74-839

Geneva Pharmaceuticals, Inc.
Attention: Beth Brannan
2555 W. Midway Blvd.
Broomfield CO 80038-0446

MAY 21 1996

Dear Madam:

Reference is made to the Abbreviated New Drug Application submitted on January 31, 1996, for Etodolac Tablets 400 mg.

The Office of Generic Drugs has reviewed the bioequivalence data submitted and the following comments are provided for your consideration:

> Dissolution should be repeated on 12 individual dosage units of the test and reference products using apparatus I (basket) at 100 rpm and all other conditions the same.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Mark Anderson, Project Manager, at (301) 594-0315. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

/S/

for Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation
and Research

cc: Date _____
ANDA 74-839, Orig File, Dup File
Div File
Field Copy
HFD-615 PRickman
HFD-650 Anderson, CST

BIO-LETTER INCOMPLETE

/S/

K. Dhariwal
R. Patnaik
M. Anderson

DRAFTED: STM 05/21/96 X:\WPFILE\BIO\FINAL\N74839.APP

MAY 20 1996

Etodolac
400 mg Tablets
ANDA #74-839
Reviewer: Kuldeep R. Dhariwal
Filename: 74839SD.196

Geneva Pharmaceuticals, Inc.
2555 W. Midway Blvd.
Broomfield, CO 80038-0446
Submission Date:
January 31, 1996

Review of Fasting and Fed Bioequivalence Studies, and Dissolution Data

The firm has submitted single-dose *in vivo* bioequivalence studies under fasting and fed conditions and dissolution data comparing its etodolac tablets, 400 mg with Wyeth-Ayerst's Lodine® tablets, 400 mg.

Introduction:

Etodolac is a pyranocarboxylic acid chemically designated as (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid. Etodolac is a nonsteroidal antiinflammatory drug with antiinflammatory, analgesic, and antipyretic properties. The drug is a racemic mixture of R- and S-etodolac, the S-form being biologically active. Both enantiomers are stable and there is no R-to-S conversion *in vivo*. Etodolac is well absorbed with a relative bioavailability of 100% when 200 mg capsules were compared with a solution. The systemic availability is at least 80% and etodolac does not undergo significant first-pass metabolism following oral administration. When administered orally, etodolac exhibits characteristics which are well described by a two-compartment model with first-order absorption. Mean (± 1 SD) peak plasma concentrations range from approximately 14±4 to 37±9 ug/mL after 200 to 600 mg single doses and are reached in 80±30 minutes. The mean plasma clearance of etodolac is 47 (±16) mL/h/kg, and terminal disposition half-life is 7.3 (±4.0) hours. Intersubject variability of etodolac plasma levels, achieved after recommended doses, is substantial.

The extent of absorption of etodolac is not affected when etodolac is administered after a meal, but the C_{max} is reduced by 50% and T_{max} increased by 1.4-3.8 hours.

Etodolac is currently marketed as Lodine^{R} manufactured by Wyeth-Ayerst and is available as 200 and 300 mg capsules and 400 mg tablets. Lodine^{R} is indicated for acute and long-term use in the management of signs and symptoms of osteoarthritis, and also for the management of pain. The recommended dose for acute pain is

200-400 mg every 6-8 hours as needed, not to exceed a total daily dose of 20 mg/kg body weight. The recommended dose for osteoarthritis is initially 800 to 1200 mg/day in divided doses, followed by dosage adjustment within the range of 600 to 1200 mg/day given in divided doses. The total daily dose of Lodine^{R} should not exceed 1200 mg. For patients weighing 60 kg or less, the total daily dose should not exceed 20 mg/kg.

Bioavailability of Etodolac Tablets, 400 mg under Fasting Conditions:

A. Objective:

To compare the plasma levels of etodolac produced after administration of the test formulation with those produced after administration of a marketed reference product, under fasting conditions.

B. Study Sites and Investigators:

Clinical and Analytical Site: (b)4 - Confidential Business

Principal Investigator: (b)4 -

Project Director:

Protocol # 10767A "Bioavailability of Etodolac Tablets, 400 mg" was approved by the Institutional Review Board (b)4 - (b)4 - Confidential

Consent Form: A copy of volunteer informed consent form used in the study is given on page 86, vol. 1.1

Study Dates: Phase I June 21-23, 1995
Phase II June 28-30, 1995

Analysis Dates: July 6- July 19, 1995

C. Study Design:

The study was designed as a randomized, two-treatment crossover bioavailability study. The study was executed in two periods with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until 24 hours postdose each period. The subjects were instructed to return to the facility for the 36 hour blood sample collection. The subjects were assigned to two sequences at random as follows:

Sequence	Subject number	Phase I	Phase II
1	2,3,5,7,9,12,13,16,17,20,21,23,25	A	B
2	1,4,6,8,10,11,14,15,18,19,22,24,26	B	A

Subject numbers 2 and 26 did not complete the study

A: Etodolac Tablets, 400 mg; Geneva Pharmaceuticals, Inc.; Lot # 6495044; Batch size: [redacted] Actual yield: [redacted] Manufacture Date: 6/13/95; Assay: 100.0%; Content Uniformity: 102.1%

B: Lodine® Tablets, 400 mg; Wyeth-Ayerst Laboratories: Lot # 9941383; Expiration Date: 11/96: Assay: 99.1%; Content Uniformity: 102.0%

Formulation of the test product is given in Table 7.

The subjects fasted for no fewer than 10 hours prior to drug administration and until 5 hours postdose. Fluids were restricted within one hour of drug administration. The drug products were administered with 240 mL of water. The subjects were dosed at 2 minute intervals and were not allowed to be supine for 4 hours postdose. Identical meals were served during both phases. Blood pressure and pulse measurements were obtained predose, 4 and 24 hours postdose. Temperature and respirations were measured predose and 24 hours postdose. Diagnostic blood and urine specimens were obtained along with the 36 hour blood sample collection postdose period II (at the end of the study).

D. Subject selection:

Twenty-six healthy male subjects were enrolled in the study. Blood samples from all subjects who completed the study were to be analyzed. Following inclusion criteria were used in selecting the subjects:

- 18-50 years of age
- no more than ±15% from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from the study based on the following criteria:

- history of serious cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal diseases or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to etodolac or other NSAID

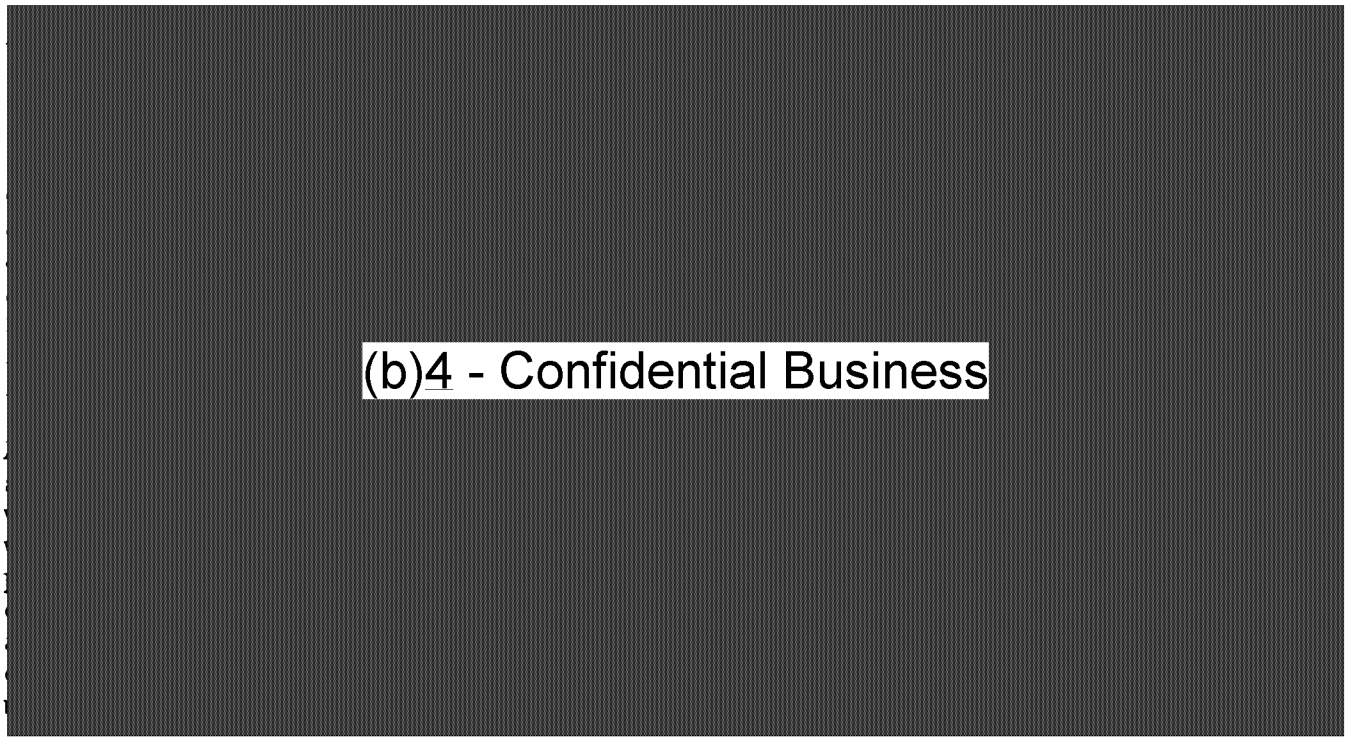
Subjects were imposed with following restrictions:

- no prescription drugs within 14 days or OTC medications (excluding ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenzes, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol administration for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- a curfew of 12 a.m. for the nights prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration
- no strenuous physical activity during the in-house portion of the study

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers® at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 24, and 36 hours postdose. Samples were centrifuged at 10°C and 2500 rpm for about 20 minutes. The plasma was transferred to prelabeled polypropylene tubes and promptly frozen at -20°C. The samples were transferred to analytical laboratory on July 5, 1995.

F. Analytical Methods:



G. Pharmacokinetics/Statistical Analysis:

Area under the concentration-time curve (AUC) was calculated by linear interpolation between consecutive drug levels. AUC_{0-t} was calculated from zero to the last non-zero concentration (C(T)). AUC_{0-inf} was calculated by extrapolation of AUC_{0-t} by C(T)/KE. The elimination rate constant (KE) was estimated by linear least squares fitting of the logarithms of the last four to six concentrations versus time. Half-life, C_{max}, and T_{max} were also calculated. The statistical analyses were performed using SAS version 6.08 and PROC GLM for the Analysis of Variance. All parameters were analyzed by ANOVA and the F-test to determine statistically significant differences (α=0.05) between the drug formulations. The 90% confidence intervals about the ratios of the test/reference means were calculated using the least squares means and the standard error of the formulation difference from the ANOVA.

H. Results:

1. Clinical:

Twenty-six subjects entered the study. Subject #2 failed to return to complete period II. Subject #26 tested positive for cocaine on June 28 (entry of period II) and was withdrawn from the study. Samples from twenty-four subjects who completed the study were analyzed. Clinical vital signs were measured before dosing and at 4 and 24 hours after dosing.

Adverse events:

Following six subjects experienced adverse events during the study. All events were mild in nature and resolved without medical intervention:

Subject #	Phase	Product	Sign/Symptom
4	II	Test	Bradycardia
8	*	Ref	Abdominal left upper quad pain
11	I & II	Ref & Test	Increased diastolic blood pressure
13	II	Ref	Bradycardia
19	I	Ref	Fatigue
24	I	Ref	Headache

* reported at entry of phase II

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
2	high blood glucose
5	high blood glucose, bilirubin in urine
6	high blood calcium
8	high blood phosphorus
10	high WBC/HPF in urine
11	nitrite and bacteria in urine
12	high blood alkaline phosphatase,bilirubin in urine
14	high blood glucose
15	high WBC/HPF in urine
16	bilirubin in urine
17	high blood glucose
18	protein in urine
23	bacteria in urine
24	high SGOT, phosphorus and triglyceride in blood
26	nitrite and bacteria in urine

Deviations in the study:

Subject numbers 5, 7, 8, and 23 did not return to the facility for 36 hour blood sample collection of period I.

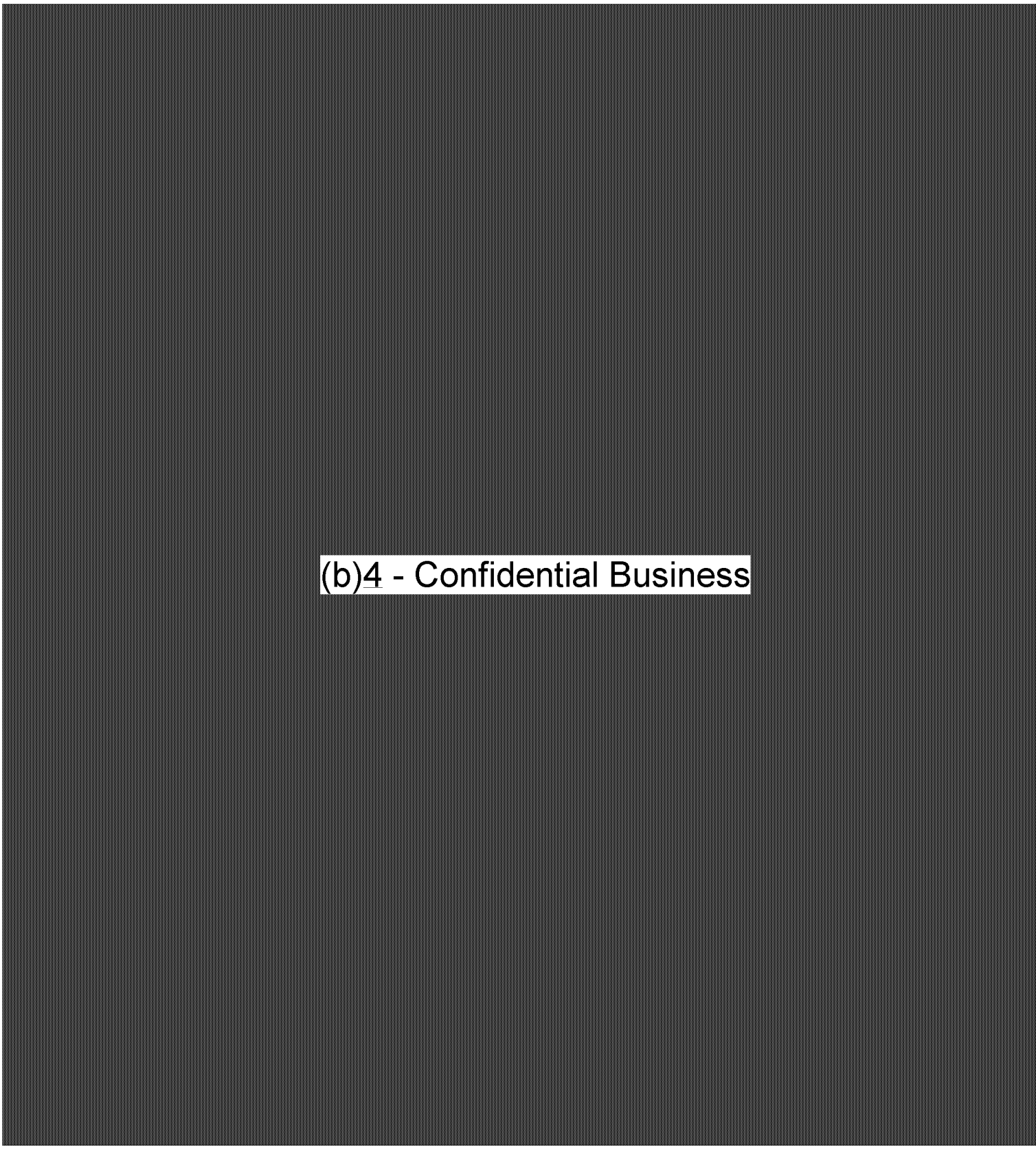
Reassays:

Of the 812 samples assayed for this study, 11 samples were reassayed. Following samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
8	Value for lowest standard concentration was uncertain during the initial run
3	Pharmacokinetic anomaly

2. Analytical:

(b)4 - Confidential Business


(b)4 - Confidential Business

(b)4 - Confidential Business

3. Pharmacokinetics/Statistics:

The mean plasma concentrations of etodolac at each time point after test and reference products are shown in Table 1. There were statistically significant differences (α=0.05) in mean concentrations at 0.33 and 4 hours after dosing. The time courses of etodolac concentration after the two products are plotted in Figure 1. The pharmacokinetic parameters are summarized in Table 2. There were no significant differences between the formulations for any parameter. Based on the least squares means, the AUC_{0-t} and AUC_{0-inf} of the test product were both 7% lower than the respective means for the reference product. The C_{max} for the test product was 9% lower than that for the reference product and occurred 20 minutes earlier. The reviewer performed some calculations to determine the accuracy of the values given in the application:

Drug Product: Etodolac (Test)

Subject #	Reviewer		Firm	
	AUC_{0-t}	AUC_{0-inf}	AUC_{0-t}	AUC_{0-inf}
3	108.98	110.31	109.0	110.3
10	205.43	216.18	205.4	216.2
20	165.39	168.36	165.4	168.4

The results of these calculations indicate good agreement between reviewer's calculations and the data reported by the firm.

The individual mean ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} are summarized in Table 3. The test/reference ratio for AUC_{0-t} ranged from [redacted] (mean 0.948), AUC_{0-inf} ranged from [redacted] (mean 0.952), and for C_{max} ranged from [redacted] with a mean of 0.939.

Table 4 shows the AUC_{0-t}/AUC_{0-inf} ratios for individual subjects. The ratios range from 0.88-0.95 for test and 0.89-0.99 for reference product.

Following are the 90% confidence intervals provided by the firm along with those calculated by the reviewer:

Parameter	90% Confidence Interval	
	Firm's values	Reviewer's values
$LNAUC_{0-t}$	87.6-99.13	87.6-99.13
$LNAUC_{0-inf}$	87.94-99.49	87.94-99.49
LNC_{max}	82.85-100.01	82.85-100.00

The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data show significant period effect for non-transformed as well as log transformed AUC_{0-t} and AUC_{0-inf}.

The first post-dose sample (0.33 h) of subject #9 on test drug had maximum plasma concentration of etodolac. This reviewer calculated 90% confidence intervals after eliminating data from this subject:

$LNAUC_{0-t}$	92.21-99.73
$LNAUC_{0-inf}$	92.77-99.99
LNC_{max}	83.19-101.15

The 90% confidence intervals for all parameters are within 80-125%.

Bioavailability of Etodolac Tablets, 400 mg: Food Study

A. Objective: (1) To compare the etodolac plasma levels produced after administration of the test formulation, with those produced after administration of a marketed reference product, when both products are administered after a standard meal

(2) To compare the etodolac plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the same test formulation, after an overnight fast

B. Study Sites and Investigators:

Clinical and Analytical Site: same as for fasting study
Principal Investi[redacted](b)4 - Confidential[redacted]
Project Director:
Protocol #10802A "Bioavailability of Etodolac Tablets, 400 mg: Effect of Food Study" was approved by the National Institutional Review Board o[redacted](b)4 - Confidential Business[redacted]
Consent Form: A copy of the volunteer informed consent form used in the study is given on page 87, vol. 1.4.
Study Dates: Period I August 4-6, 1995
Period II August 11-13, 1995
Period III August 18-20, 1995
Analysis Dates: August 31 to September 15, 1995

C. Study Design:

The protocol was designed as a randomized, single oral dose, three-treatment, three-period, six-sequence crossover bioavailability study with a one week wash-out between drug administrations. The subjects were housed in a dormitory facility from approximately 12 hours prior to drug administration until at least 24 hours after drug administration. Subjects returned to the facility for 36 hour blood draw. The subjects (who completed the study) were assigned as follows:

Subject number	Period I	Period II	Period III
1,11,14	C	A	B
2,17	B	A	C
3,12,18	B	C	A
4,7,13	A	B	C
5,10,16	A	C	B
6,8,15	C	B	A

A = Etodolac Tablets, 400 mg following a standard meal; Geneva Pharmaceuticals, Inc.; Lot #6495044
B = Etodolac Tablets, 400 mg following a standard meal; Wyeth Ayerst Laboratories; Lot #9941383
C = Etodolac Tablets, 400 mg following an overnight fast; Geneva Pharmaceuticals, Inc.; Lot #6495044

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen healthy subjects were enrolled in the study with essentially same inclusion and exclusion criteria as in the fasting study. They were subjected to same screening procedure and restrictions.

E. Study Procedure:

Treatments A and B: Subjects were given a standard breakfast after a fast lasting at least 10 hours. The breakfast was served 35 minutes prior to dosing and subjects ate the entire meal within 30 minutes. The breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 1 serving of hash brown potatoes, six fluid oz. of orange juice and eight fluid oz. of whole milk. The drug was administered with 240 mL of water.

Treatment C: Subjects were given the assigned formulation with 240 mL of water after a fast of at least 10 hours.

F. Sample Collection, Analytical Methods, and Pharmacokinetics/Statistical Analysis:

Ten milliliters of venous blood were obtained in Vacutainers with heparin anticoagulant at 0 (predose), 0.5, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, 16, 24 and 36 hours. The samples were transferred to the analytical laboratory on August 25, 1995. Analytical methods, acceptance criteria, and statistical analysis were the same as for fasting study.

G. Results:

1. Clinical:

Eighteen subjects were enrolled in the study. Seventeen subjects completed the study. Subject #9 voluntarily withdrew after completing periods I and II. Vital signs were measured at 0 (predose) and at 4 and 24 hours post-dose.

Adverse events:

Two subjects reported two adverse events:

Subj. #	Period	Product	Sign/Symptom
12	I	Ref.(fed)	Increased blood pressure
15	I	Test (fast)	Increased diastolic blood pressure

Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
3	trace leukocyte esterase & high WBC/HPF in urine
10	slight calcium oxalate crystals in urine
13	trace leukocyte esterase & high WBC/HPF in urine
17	amorphous urates in urine

Deviations in the study:

Subject #7 was inadvertently served breakfast during the fasting study in phase III. Therefore his data were not included for pharmacokinetic analysis in phase III.

There were 17 deviations in scheduled phlebotomy time, out of which 14 were due to an emergency evacuation in the building during period II:

Subj. #	Period	Product	Time Point	Deviation
1	II	Test (fed)	1.33 h	10 minutes late
			36 h	failed to return
2	II	Test (fed)	1.33 h	8 minutes late
3	II	Test (fast)	1.33 h	8 minutes late
4	II	Ref (fed)	1.33 h	6 minutes late
5	II	Test (fast)	1.33 h	5 minutes late
8	II	Ref (fed)	1 h	14 minutes late
10	II	Test (fast)	1 h	12 minutes late
11	II	Test (fed)	1 h	10 minutes late
12	II	Test (fast)	1 h	9 minutes late
			36 h	1 h 38 min. late
13	II	Ref (fed)	1 h	8 minutes late
14	II	Test (fed)	1 h	7 minutes late
15	II	Ref (fed)	1 h	5 minutes late
16	II	Test (fast)	0.5 h	3 minutes late
			1 h	5 minutes late
17	I	Ref (fed)	36 h	failed to return
	II	Test (fed)	36 h	38 minutes late

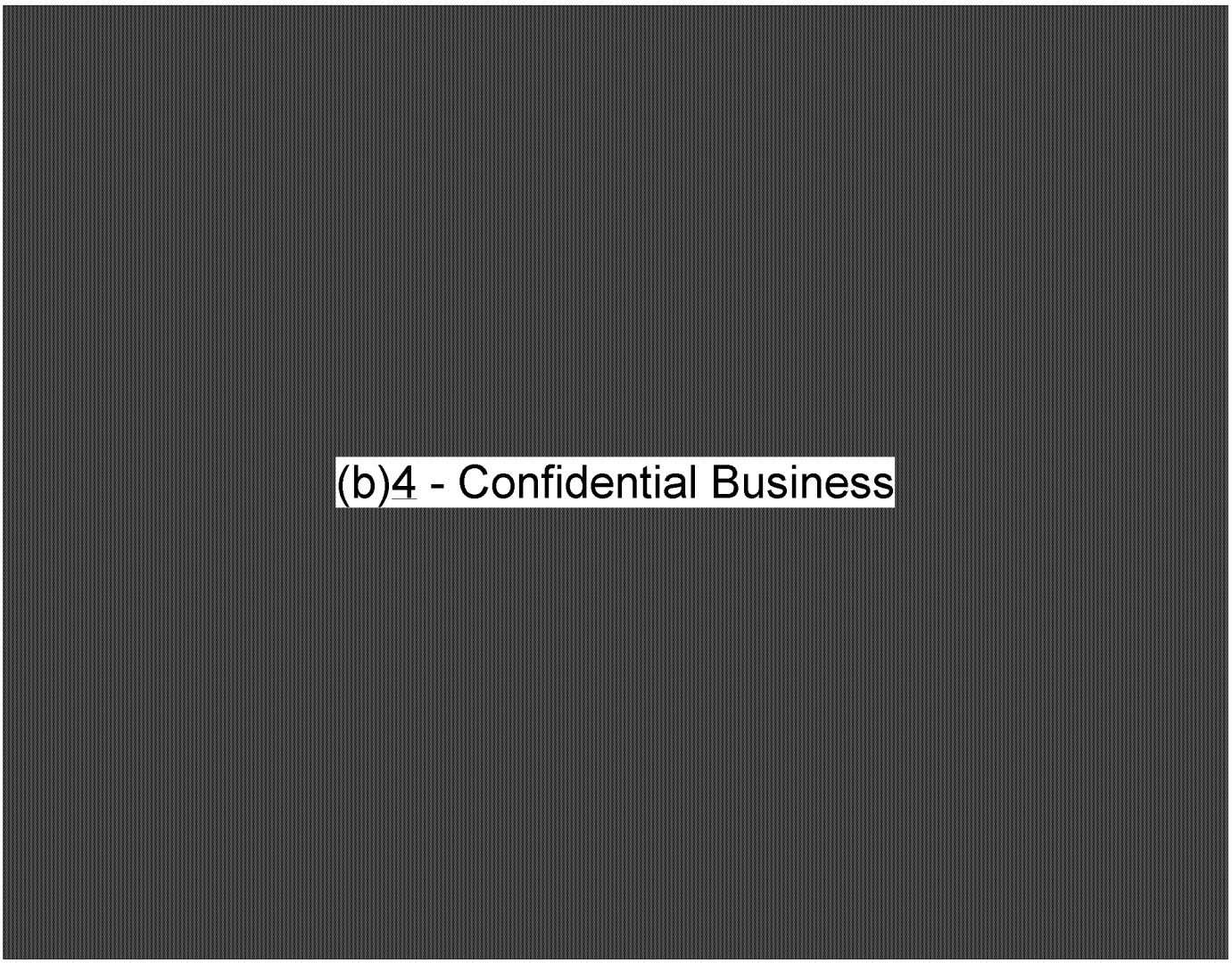
Actual times of sample collection were used for calculations. The firm has compared the differences in AUC values calculated using scheduled time vs. actual time (page 613, vol. 1.4). The differences are minimal.

Reassays:

Of the 865 samples assayed for this study, 11 samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
5	pharmacokinetic anomaly
5	suspected or documented processing error
1	to re-examine presence of peak at the retention time of the drug

2. Analytical:



3. Pharmacokinetics/Statistics:

The concentration of etodolac measured at each time point after each product is given in Table 5. From 0.5 to 2.5 hours after dosing, and at 6 and 8 hours postdose, there were significant differences in etodolac concentrations amongst the three treatments. These significant differences were a result of lower concentrations during the first 2.5 hours and higher concentrations starting at 6 and 8 hours after the doses given following a meal compared to the dose administered after an overnight fast. The time courses of etodolac concentration after the three treatments are plotted in Figure 2.

Test formulation after a meal vs. reference formulation after a meal: When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for the test formulation were 2% and 1% higher than the respective means for reference formulation. The mean C_{max} for the test product was 5% higher than that of the reference product and occurred 16 minutes earlier (Table 6).

Test formulation after a meal vs. test formulation after a 10 hour fast: The least squares means for log transformed AUC_{0-t} and AUC_{0-inf} after the meal were both 7% lower compared to 10 hour fasting. The mean C_{max} was 21% lower and 44% (34 minutes) later in test fed compared to test fasting conditions (Table 6).

Following are the ratios of the means of the pharmacokinetic parameters:

	Ratio of means (test/reference)
Test (Fed) vs. Reference (Fed)	
AUC_{0-t}	1.04
AUC_{0-inf}	1.01
C_{max}	1.05
Test (Fed) vs. Test (Fast)	
AUC_{0-t}	0.94
AUC_{0-inf}	0.93
C_{max}	0.79

Ratio of means between test fed and reference fed are within acceptable limits. The firm has provided following 90% confidence interval values for test (fed) vs. reference (fed):

AUC_{0-t}	98.10% to 106.93%
AUC_{0-inf}	96.80% to 104.86%
C_{max}	95.84% to 115.67%

Although not required for the food study, the 90% confidence intervals for these parameters are within the acceptable range of 80% to 125%.

The first post-dose sample (0.33 h) of following four subjects had maximum plasma concentration of etodolac:

Subject #	Treatment
12	test-fed
10	reference-fed
11,17	test-fasted

Following are the ratios of the means of the pharmacokinetic parameters after eliminating data from these subjects:

	Ratio of means (test/reference)
Test (Fed) vs. Reference (Fed)	
AUC_{0-t}	1.03
AUC_{0-inf}	0.96
C_{max}	1.02
Test (Fed) vs. Test (Fast)	
AUC_{0-t}	0.90
AUC_{0-inf}	0.97
C_{max}	0.80

Ratio of means between test and reference fed remain within acceptable limits.

In Vitro Dissolution Testing:

The dissolution testing was done using apparatus 2 (paddles) at 50 rpm and 1000 mL of 0.05 M pH 7.5 phosphate buffer as medium. The drug products used in the dissolution tests were from the same lot used in the *in vivo* bioequivalence studies. The firm is proposing a specification of not less than (b)4 Q) in 20 minutes. The test and reference products pass the dissolution tests using this criteria.

Comments:

Fasting Study

1. Twenty-six subjects entered the study. Subject #2 failed to return to complete period II. Subject #26 tested positive for cocaine on June 28 (entry of period II) and was withdrawn from the study. Samples from twenty-four subjects who completed the study were analyzed. Six subjects experienced adverse events during the study. All events were mild in nature and resolved without medical intervention. Fifteen subjects showed post-study laboratory results outside of the reference range and require follow-up.

2. There were no significant differences between the formulations for any pharmacokinetic parameter. Based on the least squares means, the AUC_{0-t} and AUC_{0-inf} of the test product were both 7% lower than the respective means for the reference product. The C_{max} for the test product was 9% lower than that for the reference product and occurred 20 minutes earlier. The 90% confidence intervals for AUC_{0-t}, AUC_{0-inf}, and C_{max} are within the acceptable range of 80-125%. Statistical analysis of data show significant period effect for non-transformed as well as log transformed AUC_{0-t} and AUC_{0-inf}. There was no significant treatment or sequence effect for any parameter.

3. The first post-dose sample (0.33 h) of subject #9 on test drug had maximum plasma concentration of etodolac. The 90% confidence intervals calculated by the reviewer after eliminating data from this subject were within 80-125% limit.

4. The study results demonstrate that test product is bioequivalent to reference product.

Food Study

1. Eighteen subjects were enrolled in the study. Seventeen subjects completed the study. Subject #9 voluntarily withdrew after completing periods I and II. Two subjects reported adverse events (increased blood pressure) during the study. Four subjects showed post-study laboratory results outside of the reference range and require follow-up tests and evaluation.

2. Subject #7 was inadvertently served breakfast during the fasting study in phase III. Therefore, his data were not included for pharmacokinetic analysis in phase III.

3. When the test and reference formulations were administered after a meal, the least squares means for log transformed AUC_{0-t} and AUC_{0-inf} for the test formulation were 2% and 1% higher than

the respective means for reference formulation. The mean C_{max} for the test product was 5% higher than that of the reference product and occurred 16 minutes earlier. The test/reference ratios for mean AUC_{0-t}, AUC_{0-inf}, and C_{max} are all within the 0.80-1.20 limit.

4. The least squares means for log transformed AUC_{0-t} and AUC_{0-inf} were both 7% lower when the test drug was given with food compared to 10 hour fasting. The mean C_{max} was 21% lower and 44% (34 minutes) later in test fed compared to test fasting conditions.

5. Ratio of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test fed and reference fed are within acceptable limits.

6. The first post-dose samples (0.33h) from four subjects (1 in test-fed, 1 in ref-fed, and 2 in test-fasted) had maximum plasma concentration of etodolac. The ratio of means of the pharmacokinetic parameters calculated by this reviewer after eliminating data from these subjects remained within acceptable limits.

7. The food study is acceptable.

Dissolution Testing

There is no USP method available for dissolution testing of etodolac tablets. The agency recommends following method:

Apparatus:	USP Basket
RPM:	100
Medium:	pH 7.5 Phosphate Buffer, 0.05 M
Volume:	1000 mL
Sampling Times:	5,10,20, and 30 minutes

The firm would be asked to repeat the dissolution testing using apparatus I (basket) at 100 rpm and all other conditions the same.

Deficiencies:

The firm should repeat dissolution testing on 12 individual dosage units of the test and reference products using apparatus I (basket) at 100 rpm and all other conditions the same.

Recommendations:

1. The *in vivo* bioequivalence study conducted under fasting conditions by Geneva Pharmaceuticals, on its etodolac tablets, 400 mg, lot #6495044, comparing it to the reference product Lodine® tablets, 400 mg, lot #9941383 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting

conditions, Geneva's etodolac tablet, 400 mg is bioequivalent to the reference product Lodine® tablet, 400 mg manufactured by Wyeth-Ayerst.

2. The *in vivo* bioequivalence study conducted under fed conditions by Geneva Pharmaceuticals on its etodolac tablets, 400 mg, lot #6495044, comparing it to the reference product Lodine® tablets, 400 mg, lot #9941383 manufactured by Wyeth-Ayerst has been found acceptable to the Division of Bioequivalence. The study demonstrates that under fed conditions, the bioavailability of Geneva's etodolac tablet, 400 mg is similar to that of the reference product Lodine® tablet, 400 mg manufactured by Wyeth-Ayerst.

3. The dissolution testing conducted by Geneva Pharmaceuticals is not acceptable. The firm should be advised to conduct dissolution testing on 12 individual dosage units of the test and reference products employing 1000 mL of 0.05 M Phosphate buffer pH 7.5 at 37°C using USP XXIII apparatus I (basket) at 100 rpm.

4. From the bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency but not the *in vitro* dissolution testing, and the application is not acceptable.

The firm should be informed of the deficiency and recommendations.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR /S/ Date 5/16/96

Concur: /S/ Date 5/20/96
for Keith Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #74839 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-344 (CViswanathan), HFD-655 (Nerurkar, Dhariwal), Drug File, Division File

Draft: 051396; Final 051596

Table 1

Etodolac Plasma Concentrations (μg/mL) in Fasting Study: Arithmetic Means ± Standard Deviation (N=24)

Time (h)	Test	Reference	Test/ref	Signific. at p=0.05
0	0	0	-	-
0.33	14.93±9.672	9.278±7.933	1.61	p<0.05
0.67	25.01±9.916	21.08±14.04	1.19	N.S.
1	25.81±10.16	23.18±10.74	1.11	N.S.
1.33	24.39±8.501	24.02±10.78	1.02	N.S.
1.67	24.06±6.796	22.56±9.486	1.07	N.S.
2	22.18±5.852	22.27±8.761	1.00	N.S.
2.5	19.50±5.218	20.96±7.993	0.93	N.S.
3	17.65±5.436	19.51±7.376	0.90	N.S.
4	13.97±3.881	17.59±6.091	0.79	p<0.05
6	9.062±3.045	10.29±4.250	0.88	N.S.
8	5.496±2.289	6.473±3.372	0.85	N.S.
10	5.064±2.848	5.658±3.110	0.89	N.S.
12	3.913±2.047	4.197±2.059	0.93	N.S.
16	2.414±1.167	2.656±1.334	0.91	N.S.
24	1.482±1.010	1.664±1.073	0.89	N.S.
36	0.5341±0.63	0.560±0.549	0.95	N.S.
Parameter				
AUC_{0-t} (μg/mLxh)	173.5±55.55	187.1±63.21	0.93	
AUC_{0-inf} (μg/mLxh)	182.0±65.79	195.1±70.65	0.93	
C_{max} (μg/mL)	31.53±6.240	34.47±6.720	0.91	
T_{max} (h)	1.362±1.154	1.695±1.098	0.80	
Half-life (h)	7.747±2.318	7.828±2.234	0.99	
Rate constant	0.096±0.022 (h^{-1})	0.095±0.024	1.01	

Table 2

Etodolac Plasma Concentrations in the Fasting Study (N=24)
Pharmacokinetic Parameters: Least Squares Means ± Standard Error

Parameter	Test	Reference	Test/Ref	90% Confidence Interval
AUC_{0-t} (μg/mLxh)	173.5±5.96	187.1±5.96	0.93	85-100%
AUC_{0-inf} (μg/mLxh)	182.0±6.15	195.1±6.15	0.93	86-101%
C_{max} (μg/mL)	31.53±1.13	34.47±1.13	0.91	84-99%
T_{max} (h)	1.362±0.136	1.695±0.136	0.80	61-100%
Half-life (h)	7.747±0.16	7.828±0.16	0.99	94-104%
Rate constant (h^{-1})	0.0957±0.002	0.0948±0.002	1.01	97-105%
$LNAUC_{0-t}$ (Antiln)	5.1167±0.025 (166.8)	5.1872±0.025 (179)	0.93	88-99%
$LNAUC_{0-inf}$ (Antiln)	5.1559±0.025 (173.5)	5.2227±0.025 (185.4)	0.94	88-99%
LNC_{max} (Antiln)	3.4276±0.039 (30.80)	3.5216±0.039 (33.84)	0.91	83-100%

Table 3

Test/Reference Ratios for Pharmacokinetic Parameters in the Fasting Study for Individual Subjects

Subject	Sequence	Ratio		
		AUC_{0-t}	AUC_{0-inf}	C_{max}
1	2	[redacted]		
3	1			
4	2			
5	1			
6	2			
7	1			
8	2			
9	1			
10	2			
11	2			
12	1			
13	1			
14	2			
15	2			
16	1			
17	1			
18	2			
19	2			
20	1			
21	1			
22	2			
23	1			
24	2			
25	1			
Mean		0.948	0.952	0.939
Std Deviation		0.163	0.161	0.228
CV (%)		17.14	16.97	24.29

(b)4 - Confidential Business

Table 4

AUC_{0-t}/AUC_{0-inf} Ratio for Individual Subjects in Fasting Study

Subject	AUC_{0-t}/AUC_{0-inf} Ratio	
	Test	Reference
1	(b)4 - Confidential Business	
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		
23		
24		
25		

Table 5

Etodolac Plasma Concentrations (μg/mL) in the Food Study (N=17): Arithmetic Means ± Standard Deviation (SD)

Time h	Test-Fed A	Ref-Fed B	Test-Fasted C	A/B	A/C	B/C
0	0	0	0			
0.5	5.584±8.74	5.224±7.25	15.55±11.40	1.07	0.36	0.34
1	15.30±8.95	12.71±9.31	21.26±9.93	1.20	0.72	0.60
1.33	18.09±7.77	13.75±6.78	22.09±6.20	1.31	0.82	0.62
1.67	17.70±6.51	15.68±5.42	22.75±5.94	1.13	0.78	0.69
2	17.09±5.56	15.73±5.09	21.69±5.80	1.09	0.79	0.73
2.5	16.19±3.90	14.57±4.18	19.54±4.35	1.11	0.83	0.75
3	15.24±3.31	14.47±3.57	16.63±3.89	1.05	0.92	0.87
3.5	14.41±3.00	14.33±3.78	15.14±3.43	1.01	0.95	0.95
4	14.08±3.42	14.21±5.18	14.25±3.94	0.99	0.99	1.00
6	9.974±2.72	9.866±3.48	8.681±2.65	1.01	1.15	1.14
8	5.935±2.38	6.139±2.32	5.539±1.95	0.97	1.07	1.11
10	4.692±1.89	5.029±2.26	4.633±1.76	0.93	1.01	1.09
12	3.700±1.59	3.856±1.86	3.820±1.78	0.96	0.97	1.01
16	2.615±1.53	2.502±1.28	2.628±1.29	1.05	1.00	0.95
24	1.642±1.24	1.710±1.18	1.649±1.10	0.96	1.00	1.04
36	0.610±0.62	0.549±0.69	0.610±0.63	1.11	1.00	0.90
Parameters						
AUC_{0-t} (μg/mLxh)	156.2±55.3	150.7±46.7	168.7±55.9	1.04	0.93	0.89
AUC_{0-inf} (μg/mLxh)	165.7±67.2	164.2±65.1	179.7±66.8	1.01	0.92	0.91
C_{max} (μg/mL)	22.44±4.43	21.42±4.85	28.08±6.14	1.05	0.80	0.76
T_{max} (h)	1.852±1.09	2.102±1.13	1.366±0.54	0.88	1.36	1.54
Half-life (h)	8.376±2.66	8.261±3.09	8.718±3.23	1.01	0.96	0.95
Rate constant (h^{-1})	0.088±0.02	0.093±0.03	0.087±0.02	0.95	1.02	1.07

Test (fed) and reference (fed), 36 h sample: N=16
Test (fasted): N=16 for all time points

Table 6

Etodolac Plasma Concentrations in the Food Study (N=17)
Pharmacokinetic Parameters: Least Squares Means±Standard Error

Parameter	Test-Fed	Ref-Fed	Test-Fasted*			
	A	B	C	A/B	A/C	B/C
AUC_{0-t} (μg/mLxh)	157.6±3.47	152.3±3.47	168.6±3.64	1.04	0.94	0.90
AUC_{0-inf} (μg/mLxh)	168.6±3.33	167.3±3.33	180.5±3.50	1.01	0.93	0.93
C_{max} (μg/mL)	22.44±0.90	21.46±0.90	28.57±0.95	1.05	0.79	0.75
T_{max} (h)	1.834±0.22	2.093±0.22	1.270±0.23	0.88	1.44	1.65
$LNAUC_{0-t}$ (Antiln)	5.005±0.018 (149.1)	4.981±0.018 (145.6)	5.079±0.019 (160.7)	1.02	0.93	0.91
$LNAUC_{0-inf}$ (Antiln)	5.057±0.017 (157.2)	5.050±0.017 (156.0)	5.135±0.017 (169.8)	1.01	0.93	0.92
LNC_{max} (Antiln)	3.094±0.039 (22.07)	3.042±0.039 (20.96)	3.331±0.041 (27.98)	1.05	0.79	0.75

* N=16

Table 7

Quantitative Composition of Etodolac Tablets

Ingredient	Amount/Tablet, mg
Etodolac	400.000
Polysorbate 80 NF	[redacted]
Hydroxypropyl Methylcellulose	[redacted]
Microcrystalline Cellulose NF	[redacted]
Purified Water USP	[redacted]
Croscarmellose Sodium NF	[redacted]
Colloidal Silicon Dioxide NF	[redacted]
Magnesium Stearate NF	[redacted]
Total Tablet Core Weight	[redacted]
Opadry White	[redacted]
Opadry Clear	[redacted]
Purified Water USP	[redacted]
Total Coated Tablet Weight	674.375

The reference listed drug Lodine® 400 mg Tablet contains:

[redacted]

Table 8. *In Vitro* Dissolution Testing

Drug (Generic Name): Etodolac Tablets
Dose Strength: 400 mg
ANDA No.: 74-839
Firm: Geneva Pharmaceuticals, Inc.
Submission Date: January 31, 1996
File Name: 74839SD.196

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.05 M Phosphate Buffer, pH 7.5 Volume: 1000 mL
Specifications: NLT (b)4 Q) in 20 min.
Reference Drug: Lodine® Tablets (Wyeth-Ayerst)
Assay Methodology: (b)4 -

II. Results of *In Vitro* Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # 6495044 Strength(mg) 400			Reference Product Lot # 9941383 Strength(mg) 400		
	Mean %	Range	%CV	Mean %	Range	%CV
5	91	(b)4 - onfident Busines	6.7	20	(b)4 - onfidenti Business	22.0
10	94		3.5	49		12.7
15	96		3.0	74		10.3
20	98		1.6	90		7.0
30	99		0.9	101		1.3

Sampling Times (Minutes)	Test Product Lot # Strength(mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%CV	Mean %	Range	%CV

Figure 1: Mean Etodolac Plasma Levels

#005 – 28 – 10767

N = 24

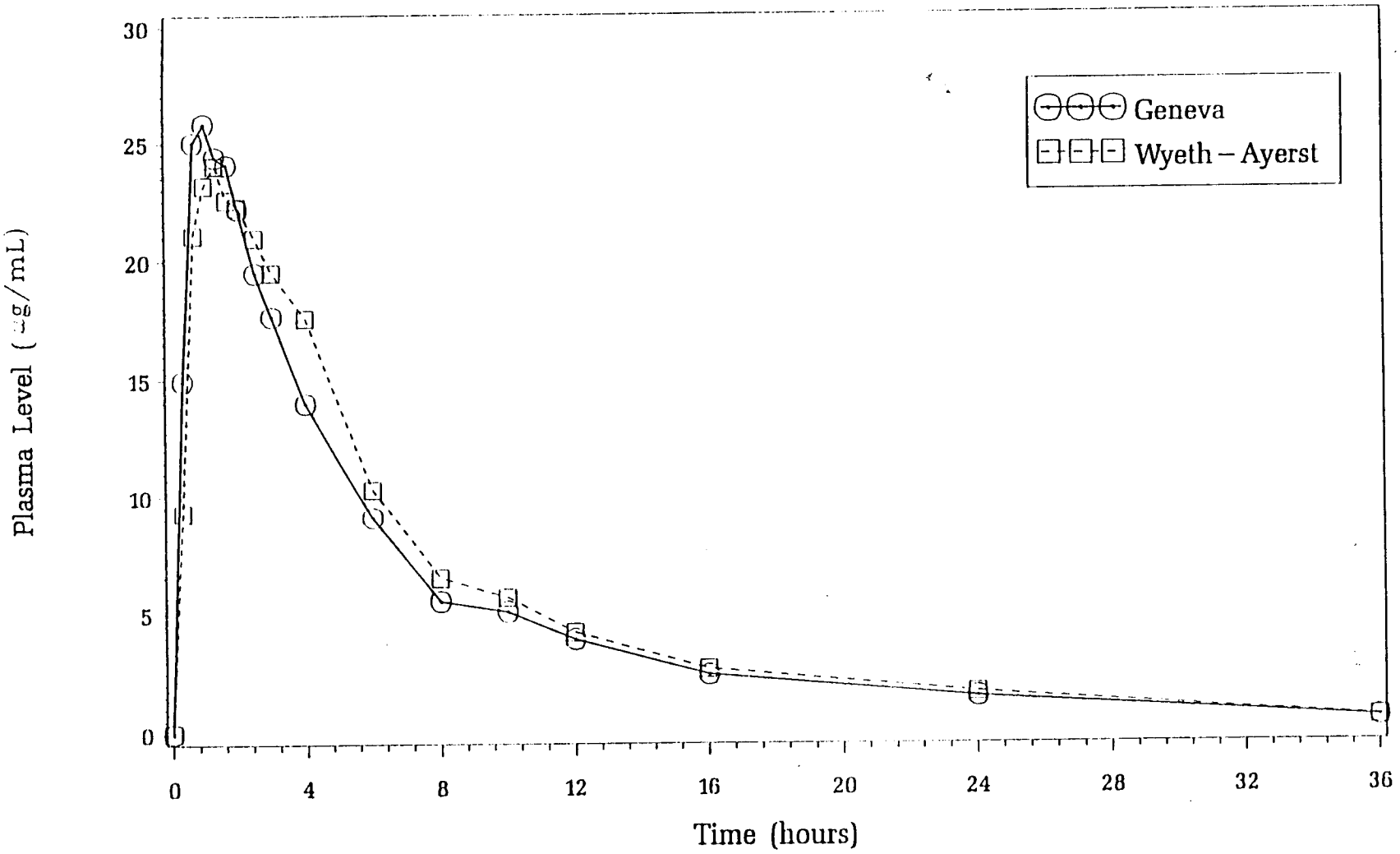


Figure 1

Figure 1: Mean Etodolac Plasma Levels

#005 – 29 – 10802

N = 17

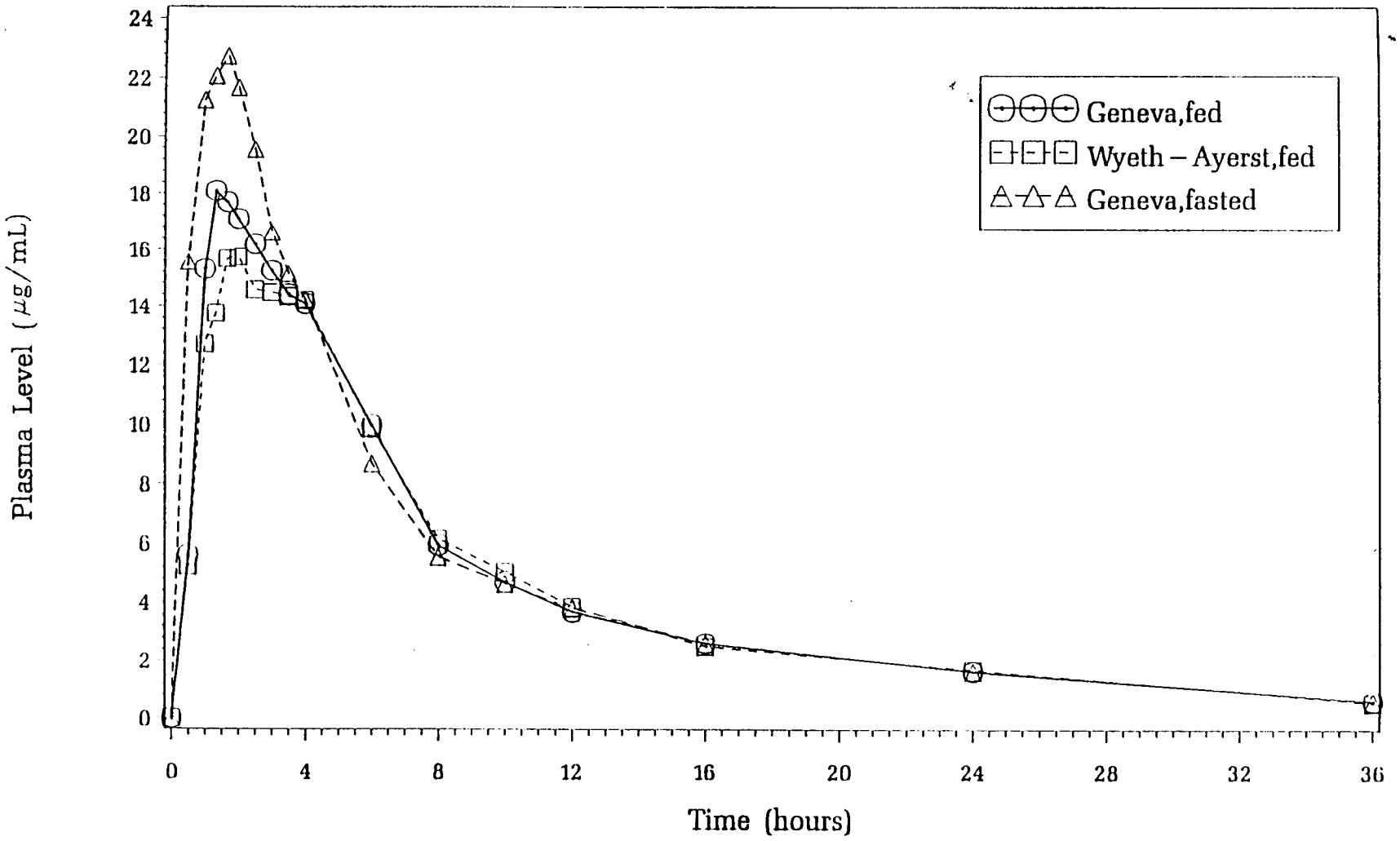


Figure 2